Taliglucerase Alfa (ELELYSO™)
National Drug Monograph
Abbreviated Review
May 2013

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section of the PBM INTRAnet (http://vaww.pbm.va.gov).

Introduction[1-7]

Taliglucerase alfa for injection (ELELYSO™), a hydrolytic lysosomal glucocerebroside-specific enzyme, was approved by the U.S. Food and Drug Administration (FDA) May 1, 2012 for long-term enzyme replacement therapy (ERT) for adults with a confirmed diagnosis of Type 1 Gaucher disease. Taliglucerase alfa is the active form of the enzyme beta- glucocerebrosidase and is produced by recombinant DNA technology using carrot plant cell culture.[1]

Type 1 Gaucher disease is an autosomal recessive disorder due to an insufficiency of the lysosomal enzyme beta-glucocerebrosidase, leading to accumulation of the lipid glucocerebroside in the lysosome of macrophages, resulting in foam cells, also referred to as Gaucher cells. In type 1 Gaucher disease, accumulation of these Gaucher cells occurs in the liver, spleen, bone marrow, as well as other organs including the lungs, resulting in hepatosplenomegaly, anemia, thrombocytopenia, pulmonary disease, and bone abnormalities including fractures and arthritis. Type 1 is the most common form of Gaucher disease and may manifest itself during childhood (with nearly half diagnosed by age 10) or anytime up through adulthood. Types 2 and 3 Gaucher disease are characterized by affecting the central nervous system. The prevalence of Gaucher disease is estimated to be 1 in 57,000 live births, with type 1 having a higher prevalence in people of Ashkenazi (eastern and central European) Jewish descent.[2-4]

Current pharmacologic treatment for Gaucher disease includes ERT, which in addition to taliglucerase alfa, includes velaglucerase alfa, a glycoprotein formed by gene activation in human fibroblasts, which has the same amino acid sequence as glucocerebrosidase;[5] and imiglucerase, an analogue of beta-glucocerebrosidase produced by recombinant DNA technology using Chinese hamster ovary cells.[6] Both of these agents are available nonformulary in the VA. Miglustat, a glucosylceramide synthase inhibitor (i.e., substrate reduction therapy or SRT) is an oral formulation for the treatment of mild to moderate type 1 Gaucher disease, and is also available nonformulary and is recommended for patients where ERT is not an option (e.g., due to allergy, hypersensitivity, or poor venous access).[7]

Summary of Clinical Trial Data[1,8,9]

The approval for taliglucerase alfa was based on data from the following clinical trials in patients with type 1 Gaucher disease; one published trial evaluating two different doses of taliglucerase alfa,[1,8,9] with an extension trial component;[1] the second an unpublished trial in patients previously treated with imiglucerase who were switched to taliglucerase alfa.[1,9]

Taliglucerase alfa, at the studied doses of 30 units/kg or 60 units/kg every other week, significantly decreased the primary endpoint of spleen volume compared to baseline in treatment-naïve patients with Gaucher disease. There was also a benefit seen with treatment in the secondary endpoints of a reduction in liver volume, increase in hemoglobin, and increase in platelet counts compared to baseline. Results of the secondary endpoints were significant compared to baseline for both doses with the exception of the increase in platelet count with the 30 units/kg dose taliglucerase alfa. Details are provided in the Table below.[8] No serious adverse events were reported in either treatment group. Treatment-related adverse events were reported in 3 patients receiving the 30 unit/kg dose (abdominal pain, feeling hot, muscle spasms, dizziness, pruritus in 1 patient; hypersensitivity in 1 patient; headache in 1 patient) and in 5 patients receiving the 60 unit/kg dose (hypersensitivity in 1 patient; arthralgia in 1 patient; headache in 1 patient; glycosuria in 1 patient; pruritus in 1 patient; skin irritation in 1 patient). Two patients, one from each group, developed IgG antibodies to taliglucerase alfa (non-neutralizing). Three patients withdrew from the study, two after hypersensitivity reactions (1 occurred immediately without receiving the first full dose), and one

due to pregnancy; therefore, 32 patients were included in the safety analysis and 31 patients in the efficacy analysis.[8] Twenty-six patients were included in the extension study and were continued at their respective doses for a total duration of 24 months. Spleen and liver volume continued to decrease and hemoglobin and platelet counts continued to increase in both treatment groups and no new safety concerns were noted.[1,9]

In Study 2, where patients previously treated with imiglucerase were switched to treatment with taliglucerase alfa, the efficacy parameters measured including spleen and liver volume and hemoglobin and platelet counts remained stable throughout the 9 months of treatment (refer to data in Table below). One patient required an increase in dose of taliglucerase alfa to 19 units/kg at week 24 (from 9.5 units/kg imiglucerase) due to a platelet count of 92,000 mm^3 at week 22 which increased to 170,000 mm^3 at 9 months.[1,9] It was reported that one patient experienced a hypersensitivity reaction.[9]

<table>
<tr><th>Clinical Trial</th><th>Inclusion</th><th>N</th><th>Duration</th><th>Treatment</th><th>Results</th></tr>
<tr><td>Study 1[8]
R, DB, PG, MC</td><td>Type 1 Gaucher disease, splenomegaly, thrombocytopenia</td><td>32

Mean age 36 (19 to 74)

48% male</td><td>9 months</td><td>TLG 30 u/kg (N=15)

TLG 60 u/kg (N=16)
every other wk</td><td>
<table>
<tr><th>Δ BL[a]</th><th>30 u/kg</th><th>60 u/kg</th></tr>
<tr><td>↓ SV[b]</td><td>26.9%</td><td>38.0%</td></tr>
<tr><td>↓ LV[c]</td><td>10.5%</td><td>11.1%</td></tr>
<tr><td>↑ Hgb[d]</td><td>1.6</td><td>2.2</td></tr>
<tr><td>↑ Plt[e]</td><td>11,427</td><td>41,494</td></tr>
</table>
</td></tr>
<tr><td>Study 2[1]
OL, SA, MC</td><td>Type 1 Gaucher disease, ≥ 2 yrs IMG 11 to 60 u/kg with stable dose x 6 months</td><td>25

Mean 45 (13 to 66)

46% male</td><td>9 months</td><td>Switch from IMG to TLG at same dose; dose adjustments per protocol</td><td>
<table>
<tr><th></th><th>IMG (BL)</th><th>TLG</th></tr>
<tr><td>SV[f]</td><td>5.5</td><td>5.1</td></tr>
<tr><td>LV[f]</td><td>1.0</td><td>0.9</td></tr>
<tr><td>Hgb[g]</td><td>13.6</td><td>13.4</td></tr>
<tr><td>Plt[g]</td><td>160,447</td><td>165,654</td></tr>
</table>
</td></tr>
</table>

For Study 1: Gaucher disease diagnosis=leukocyte glucocerebrocidase activity ≤ 3 nmol/kg*hr; splenomegaly= > 8x expected volume; thrombocytopenia=platelet counts < 120,000 mm^3 with or without anemia
BL=baseline; DB=double-blind; Hgb=hemoglobin; IMG=imiglucerase; LV=liver volume; MC=multicenter; NS=not statistically significant; OL=open-label; Plt=platelet count; R=randomized; SA=single-arm; SV=spleen volume; TLG=taliglucerase alfa; yrs=years
[a] Baseline: mean SV 30 u/kg 2134 ml (reported as 15.4 multiples of normal in the product prescribing information), 60 u/kg 2117 ml (reported as 16.7 multiples of normal in the product prescribing information); mean LV 30 u/kg 2880 ml, 60 u/kg 2481 ml; mean Hgb 30u/kg 12.2 g/dL, 60u/kg 11.4 g/dl; mean Plt 30 u/kg 75,320, 60 u/kg 65,038
[b] Primary endpoint: 30 u/kg P<0.0001; 60 u/kg P<0.0001; 60u/kg vs. 30u/kg P=0.021; there was a mean reduction in SV of 4.5 multiples of normal in the 30 u/kg group and of 6.6 multiples of normal in the 60 u/kg group per the product prescribing information
[c] 30 u/kg P=0.004; 60 u/kg P<0.0001; 60u/kg vs. 30u/kg NS
[d] 30 u/kg P=0.001; 60 u/kg P<0.0001; 60u/kg vs. 30u/kg NS
[e] 30 u/kg NS; 60 u/kg P=0.003; 60u/kg vs. 30u/kg P=0.042
[f] reported as multiples of normal
[g] mean values

Safety[1]

Contraindications: There are no known contraindications to taliglucerase alfa.[1]

Warnings and Precautions: Taliglucerase alfa is an intravenous glycoprotein and therefore has the potential for causing severe allergic reactions. Anaphylaxis has been reported in patients receiving taliglucerase alfa. If anaphylaxis occurs, the medication should be promptly discontinued with implementation of appropriate medical management. Caution should be used in patients with previous anaphylaxis on taliglucerase alfa who are being rechallenged, and medical support should be available. Infusion reactions, including allergic reactions, are the most common adverse reaction with taliglucerase alfa, occurring in 44 to 46% of patients in clinical trials. Symptoms of infusion reactions included headache, chest pain or discomfort, asthenia, fatigue, urticaria, erythema, increased blood pressure, back pain and arthralgia, flushing, angioedema, wheezing, dyspnea, coughing, cyanosis, and hypotension. It is recommended that the severity of the infusion reaction can be used to determine the management (e.g., slowing the infusion rate or treatment with antihistamines or antipyretics). Pre-treatment with corticosteroids and/or antihistamines may be considered in patients who previously required treatment for infusion reactions with taliglucerase alfa.

Adverse Reactions: The following adverse events occurring in ≥ 10% of patients treated with taliglucerase alfa in patients who were treatment-naïve (N=32) and in those who were switched from imiglucerase (N=28), respectively, are as follows: infusion reaction (44%, 46%); upper respiratory tract infection/nasopharyngitis (22%, 18%); pharyngitis/throat infection (19%, 4%); headache (19%, 11%); arthralgia (13%, 11%); influenza/flu (13%, 4%);

urinary tract infection/pyelonephritis (9%, 11%); back pain (3%, 11%); extremity pain (0, 11%). Adverse reactions reported in > 2% of patients in clinical trials included: fatigue, pain, pharyngolaryngeal pain, pruritus, diarrhea, dizziness, nausea, bone pain, abdominal pain, erythema, flushing, peripheral edema, muscle spasms, paresthesia, dyspnea, throat irritation, asthenia, chest discomfort, infusion site pain, increased alanine aminotransferase, musculoskeletal discomfort, musculoskeletal pain, insomnia, rash, and skin irritation. A Type III immune-complex mediated hypersensitivity skin reaction was reported in one patient.[1]

Immunogenicity: In a study of treatment-naïve patients, 17 of 32 (53%) patients developed IgG anti-drug antibodies to taliglucerase alfa. Two additional patients had positive antibodies at baseline, with one patient discontinuing therapy after an allergic reaction after one dose and the other with increasing antibodies during continued treatment. In the study of patients previously treated with imiglucerase, 4 of 28 patients (14%) developed IgG anti-drug antibodies after being switched to taliglucerase alfa. One additional patient had positive antibodies at baseline but did not have increased titers with continued therapy. It is unknown if the presence of IgG anti-drug antibodies increases the risk for infusion reactions. It is recommended that anti-drug antibodies to taliglucerase alfa be monitored in patients with infusion reactions, and in patients who previously experienced infusion reactions with other ERTs. Three patients tested positive for neutralizing antibodies (per *in vitro* assays); however, the clinical significance is unknown at this time.[1]

Pregnancy and Nursing Mothers: Taliglucerase alfa is pregnancy category B. There were no adverse effects noted in animal studies; however, since pregnancy studies with taliglucerase alfa have not been conducted in humans, it is recommended that taliglucerase alfa not be prescribed during pregnancy unless felt to be clinically necessary. As there are no data in lactating females and it is unknown if taliglucerase alfa is excreted in human milk, caution should be used if taliglucerase alfa is used in nursing women.[1]

Look-alike/Sound-alike (LA/SA) Error Risk Potential

As part of a Joint Commission standard, LA/SA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Taliglucerase alfa	None	None	None	Alglucerase Velaglucerase Imiglucerase Agalsidase alfa Agalsidase beta Alglucosidase alfa
ELELYSO™	None	None	None	Elaprase Elestat

Dosage and Administration[1]

Taliglucerase alfa is available in 200 unit single-use vials for reconstitution. The recommended dose of taliglucerase alfa is 60 units/kg every 2 weeks, administered as an intravenous infusion over 60 to 120 minutes under the supervision of a healthcare professional. Dose adjustments should be individualized according to patient response and therapeutic goals. Doses used in clinical trials have been from 11 units/kg to 73 units/kg, administered every other week.

The following recommendations for preparation and administration under aseptic technique are provided by the manufacturer:[1]

- Determine the number of vials to be reconstituted according to the dose calculated based on the patient's weight and remove from the refrigerator (vials should not be left at room temperature for more than 24 hours prior to reconstitution; vials should not be heated or microwaved)
- Reconstitute each vial with 5.1 ml sterile water for injection , for a withdrawal volume of 5 ml
- Gently mix (DO NOT SHAKE) the vials and inspect for particulate matter; the solution should be colorless and clear

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- Withdraw 5 ml from each vial and dilute with 0.9% sodium chloride injection to a final volume of 100 to 200 mlfor IV administration; gently mix (DO NOT SHAKE) the content of the final solution to be administered (slight flocculation may occur after dilution)
- The initial infusion rate should be 1.3 ml/min until patient tolerability has been established, after which time the rate may be increased to 2.3 ml/min. The total volume of the infusion should be administered over a period of no less than 60 minutes, using low-protein binding containers and administered with a low-protein binding infusion set with an in-line low protein-binding 0.2 micrometer filter
- Taliglucerase alfa is preservative-free and once reconstituted, should be administered immediately. If this is not possible, the reconstituted product or diluted solution may be stored for up to 24 hours at 2 to 8° C (36 to 46° F; do not freeze) and protected from light; any unused product should be discarded

Instructions for Special Handling

Instructions for obtaining taliglucerase alfa (ELELYSO) are available on the PBM INTRAnet under Special Handling Drugs.

Acquisition Cost

Refer to VA pricing sources for updated information.

Conclusions

According to published data, treatment with taliglucerase alfa at the approved dose improved disease-related parameters including spleen volume, liver volume, anemia, and thrombocytopenia in patients with type 1 Gaucher disease and, per unpublished data, is continued with treatment up to 24 months. According to unpublished data, it appears that the benefit of therapy is maintained when patients are switched from imiglucerase to comparable doses of taliglucerase alfa. Published quality of life data with taliglucerase alfa are not available. At this time, there are no direct comparison trials to determine if there are differences in clinical outcomes or adverse events with taliglucerase alfa compared to treatment with velaglucerase alfa or imiglucerase.

It would be expected that the prevalence of type 1 Gaucher disease in the Veteran population would be very low. Under these circumstances, it would be anticipated that utilization of treatments for this condition would be minimal.

References

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9. Hollack CEM. An evidence-bassed review of the potential benefits of taliglucerase alfa in the treatment of patients with Gaucher disease. Core Evidence 2012;7:15-20.

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